
Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**February 2016
Clinical/Medical**

Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

*Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

and/or

*Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration*

*10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov*

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**February 2016
Clinical/Medical**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	SELECTIVE SAFETY DATA COLLECTION	3
A.	Types of Clinical Investigations That May Be Considered for Selective Safety Data Collection.....	4
B.	Types of Safety Data That May Be Appropriate for Selective Safety Data Collection	5
C.	Other Considerations for Safety Data Collection	6
D.	Types of Safety Data That Should Always Be Collected	6
IV.	METHODS FOR SELECTIVE SAFETY DATA COLLECTION	7
V.	AGREEMENT BETWEEN SPONSORS AND FDA ON A PLAN FOR SELECTIVE SAFETY DATA COLLECTION	8

Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help sponsors determine the amount and types of safety data to collect during late-stage premarket and postapproval clinical investigations, (e.g., phase 3 clinical trials, studies of new uses, long-term outcomes). This guidance discusses a selective approach to safety data collection during late-stage premarket development or during the postapproval stage based on what is already known about a drug's² safety profile. This guidance provides recommendations on when to consider selective safety data collection and how to do so to maintain a balance between eliminating the collection of data that will not be useful and collecting sufficient data to allow adequate characterization of the safety profile of a drug. In addition, this guidance provides information to sponsors about consulting with the relevant FDA review division or divisions to determine whether a selective approach to safety data collection would be appropriate (see section V of this guidance).

This guidance is intended to apply to safety data collection during late-stage premarket and postapproval clinical investigations in all disease settings except rare diseases (see section III of this guidance). There is an existing FDA guidance that applies to the collection of clinical data in all phases of oncology clinical trials,³ but that guidance does not discuss selective safety data

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² For the purposes of this guidance, all references to *drugs* or *drug products* include both human drugs and biological drug products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research unless otherwise specified.

³ See the guidance for industry *Cancer Drug and Biological Products – Clinical Data in Marketing Applications*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

collection in the specific instances covered in this guidance. For this reason, the recommendations in this guidance may differ from those in the oncology-focused guidance. Where differences occur, the recommendations in this guidance apply.

FDA is also aware that some of the recommendations in this guidance may not align with the expectations of safety data collection in other regions or countries, which may lead to difficulty in implementing this guidance in some clinical investigations. However, we believe this guidance will give sponsors the flexibility to design and implement protocols with selective safety data collection where appropriate.

This guidance is not intended to affect reporting (as opposed to collection) of postmarketing adverse events relevant to an approved drug as required under 21 CFR 314.80 and 600.80 or affect reporting of investigational new drug application (IND) safety information as required under § 312.32 (21 CFR 312.32).⁴ Those reporting requirements remain unchanged, and selective safety data collection may only occur in a manner that would permit all regulatory reporting requirements to be fulfilled.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A robust safety database is critically important to accurately assess and adequately characterize the risks of a new drug. Sponsors collect extensive safety-related data throughout the course of drug development, and knowledge about a drug's safety profile continually evolves as safety data accumulate. Comprehensive safety data, including essentially all adverse events, are collected in the early stages of drug development. In the later stages of premarket development or in postapproval studies or clinical trials, it may be appropriate to use a selective approach to safety data collection for common, non-serious adverse events that have already been well-characterized through data collection in earlier stages. For example, if safety data already collected on hundreds of patients indicate that 17 percent reported a headache when on drug treatment compared with 10 percent on placebo, collection of similar data in thousands of additional patients in a large phase 3 trial would minimally refine this value and would require extensive resource utilization, while providing no important new information. In this situation, a limited collection of safety data may be appropriate.

⁴ FDA's final rule discusses the rationale for more-selective use of IND safety reports (*Investigational New Drug Safety Reporting for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans* (75 FR 59935, September 29, 2010)).

The guidance for industry and investigators *Safety Reporting Requirements for INDs and BA and BE Studies* also discusses FDA's thinking on reporting information that is interpretable and that will meaningfully contribute to a drug's safety profile. (IND means investigational new drug application; BA and BE means bioavailability/bioequivalence).

Contains Nonbinding Recommendations

Encouraging selective safety data collection in late-stage premarket and postapproval clinical investigations is consistent with FDA's overall approach to safety assessment, which focuses on information that is useful and adds to existing knowledge. For example, § 312.32 requires expedited reporting of serious, unexpected suspected adverse reactions to FDA and all investigators during drug development.

In some cases, collection of data that do not contribute to better characterizing the safety profile of a drug may have negative consequences. For example, there is growing interest in larger, simpler trials to obtain outcome data, data on long-term effects of drugs, and data on comparative effectiveness and safety. Excessive safety data collection may (1) discourage the conduct of these types of trials by increasing the resources needed to perform them and (2) be a disincentive to investigator and patient participation in clinical trials. Thus, selective safety data collection may (1) facilitate the conduct of larger trials without compromising the integrity and the validity of trial results or losing important information, (2) facilitate investigators' and patients' participation in clinical trials, and (3) help contain costs by making more-efficient use of clinical trial resources. For these reasons, selective safety data collection should be considered in circumstances where it is appropriate (see section III of this guidance).

III. SELECTIVE SAFETY DATA COLLECTION

If the drug's safety profile has already been well-established, selective safety data collection may be appropriate during late-stage premarket and postapproval clinical investigations. Examples of selective safety data collection include, but are not limited to, the following:

- No collection of certain safety data
- Less-frequent collection of certain safety data
- Collection of certain safety data from only a fraction of the total trial enrollment (e.g., 10 percent of patients in a large trial)

In general, selective safety data collection may be appropriate for certain types of safety data when the following conditions are met:

- The number of patients and their characteristics, the duration of exposure, and the dose range used in previous clinical investigations are sufficient to adequately characterize the safety profile of the drug for common, non-serious adverse events.
- The occurrence of common, non-serious adverse events has been generally similar across multiple clinical investigations.
- The drug's safety profile is established to the extent that it is reasonable to conclude that the occurrence of common, non-serious adverse events in the population to be studied will be similar to rates observed in previously conducted clinical investigations.

Contains Nonbinding Recommendations

For clinical investigations in which these conditions are met, the amount and types of data appropriate for selective safety data collection will vary depending on a range of factors, including the disease being studied, the patient population, subgroup or subgroups of interest, nonclinical findings, prior experience with the drug and drug class, and study design.

A. Types of Clinical Investigations That May Be Considered for Selective Safety Data Collection

Selective safety data collection may be appropriate in the following types of clinical investigations. However, these are not the only circumstances where selective safety data collection may be appropriate, and this is not intended to be a complete list.

- **Clinical investigations of new indications of approved drugs:** Selective safety data collection may be appropriate in clinical investigations for new indications if the existing safety database is relevant to such investigations, including, for example, the similarity of the population studied in the new investigation to patients previously studied and the doses used.
- **Postapproval clinical studies and trials conducted to fulfill postmarketing requirements and postmarketing commitments:** When the study population in these types of studies or trials is generally the same as or is similar to the population from which the premarket safety database was derived, safety data collection can often be limited to the primary safety endpoint and other endpoints of interest.
- **Late-stage premarket and postapproval outcome clinical trials:** Outcome clinical trials usually involve relatively large populations (often 5,000–15,000 patients) similar to populations previously studied and are usually of longer duration than earlier studies. Typically, a fairly substantial safety database is in existence before initiation of an outcome clinical trial, and this database already provides sufficiently precise estimates of common, non-serious adverse events (e.g., those that occur in 5 percent or more of exposures). Even when there is not extensive prior safety data, full data could be collected in a subset of patients (e.g., 1,000) with more-selective data collection in other patients.
- **Premarket clinical investigations for some original applications:** Unless sufficient safety data already exist to adequately characterize the safety profile of a drug, comprehensive safety data collection is expected throughout premarket clinical development intended to support approval of a new drug application (NDA) or a biologics license application (BLA) for a novel agent in order to elucidate occurrence, dose-response, and subset (demographic, concomitant illnesses, concomitant therapy) variations for the full range of adverse events of the drug. However, even in a development program for a novel agent, if sufficiently comprehensive safety data become available before completion of clinical development, selective safety data collection in some late-stage investigations may be appropriate. For example, selective safety data collection may be appropriate in phase 3 trials where the existing

Contains Nonbinding Recommendations

safety database adequately characterizes a drug's safety for more common, non-serious adverse events; therefore, data on those events may not need to be collected.

- **Postapproval clinical investigations in a different patient population or with different doses or other conditions of use:** Selective safety data collection generally may not be appropriate in clinical investigations of marketed drugs in which there are important differences in the patient population, dose, dosage regimen, duration of use, or route of administration compared with the conditions of use for the marketed indications. For example, the safety database of a drug approved to treat active cancer generally would not be adequate to permit selective safety data collection in an investigation of the long-term use of that drug for adjuvant therapy or in the prevention of cancer in a healthy population. Even in this setting, however, it may be appropriate, in some cases, to collect common, non-serious adverse events in only a subset of the overall study population. An exception may also apply in cases where a lower dose or shorter duration of therapy is being investigated.

B. Types of Safety Data That May Be Appropriate for Selective Safety Data Collection

Where selective safety data collection is suitable, it may be appropriate to limit collection of data or stop collection of certain types of data, including the following:

- **Non-serious adverse events not associated with dose modification, drug discontinuation, or withdrawal from the trial:** Generally, these events are well-characterized when a drug is far along in development or has obtained marketing approval, and additional data collection would be unlikely to add to the established safety profile of a drug.
- **Routine laboratory monitoring:** In many cases, it may be possible to eliminate routine laboratory monitoring or to decrease the frequency of monitoring certain laboratory parameters (e.g., less-frequent liver function testing as safety profile data diminish concerns about hepatotoxicity).
- **Information on concomitant medications:** If existing data satisfactorily characterize all anticipated drug-drug interactions and metabolic pathways, additional detailed information on concomitant medications (e.g., dose, dosing schedule, start and stop dates) may be of limited use, particularly for drugs used only short term.
- **Patient history and physical exams:** Less-detailed histories and less-frequent physical exams for patients may be appropriate in some circumstances, especially in outcome clinical trials. If an abbreviated history is considered appropriate but certain aspects of the history are considered relevant and should be collected (e.g., cardiovascular disease, psychiatric history, including history of depression, suicidality, or both), these aspects should be described in the protocol.

Contains Nonbinding Recommendations

C. Other Considerations for Safety Data Collection

For situations that may be appropriate for selective safety data collection, sponsors should nonetheless consider where there may be reasons to collect complete data to better characterize the safety profile of a drug. This may apply even for adverse events that are not serious, fatal, or dose-modifying or that do not cause drug discontinuation or withdrawal from the trial. For example:

- **Collection of complete safety data in population subsets:** If availability of data in a subset of a population is limited, generally all data on use of a drug in these specific populations should be collected (including data on non-serious adverse events). For example, information on exposure in pediatric patients, pregnant and nursing women, and geriatric populations is often limited, so that selective safety data collection may not be appropriate in those populations.
- **Collection of complete safety data to identify risk factors:** The incidence and severity of an adverse event may be related to baseline factors and other aspects of treatment. For this reason, where there is a known or suspected causal relationship between a drug and an adverse event, it may be important to continue collecting complete safety information throughout drug development to better characterize the relationship and the effect of these influences (e.g., baseline risk or demographic factors, dose-response, drug concentration, concomitant therapy, concomitant illness) on risk.

D. Types of Safety Data That Should Always Be Collected

Sponsors should be aware that the following types of data are generally not appropriate for selective safety data collection and should always be collected:

- Data on all serious adverse events.
- Data on non-serious adverse events that lead to dose modification, drug discontinuation, or withdrawal from the trial.
- Data on unscheduled study visits, hospitalizations, and accidental injuries because these events may reflect serious adverse events of the drug.
- In an oncology setting, data from all Grade 3 and Grade 4 adverse events, as well as Grade 2 adverse events that affect vital organs (e.g., heart, liver).^{5,6}

⁵ The grading system was used for adverse events in cancer trials described in the Common Terminology Criteria for Adverse Events document from the National Cancer Institute (U.S. Department of Health and Human Services' National Cancer Institute at the National Institutes of Health). The grading system is accessible at <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> (under the heading "Files: Booklet").
A Grade 4 adverse event results in the need for life-saving and urgent intervention.

Contains Nonbinding Recommendations

- In development programs for rare disease indications, complete safety data should be collected, because these trials generally have limited patient populations and are unlikely to meet the recommendations for selective safety data collection.

For these types of safety data, it is generally important to collect information on all occurrences to better understand the following:

- Causality
- Incidence
- Severity of adverse events
- Populations that are at risk
- Dose-response
- Other factors that contribute to our understanding of the nature of the event and who is at risk

IV. METHODS FOR SELECTIVE SAFETY DATA COLLECTION

Apart from not collecting certain safety data, a plan for selective safety data collection could include the following modifications as appropriate:

- **Limiting safety data collection to a pre-identified subset of study population:** It may be appropriate to collect certain safety data (e.g., non-serious adverse events) from a sample of the study population. Methods for selecting the subpopulation should be detailed in the protocol. These may include selecting patients randomly, selecting study sites randomly, or selecting only the larger population sites. When selecting patient subsets or sites, it may be important to ensure representation from important demographic or disease-specific subgroups.
- **Decreasing the frequency of data collection:** Less-frequent collection of specific safety data, such as laboratory data and physical examination data, may be appropriate for long-term trials of drugs with substantial short-term exposure. For example, laboratory studies and physical-examination data may be collected at relatively long intervals (e.g., every 6 months). Telephone and online follow-up between study visits may help maintain contact with patients.

Specific safety data that will not be collected for the selective collection plan should be listed in the protocol.

A Grade 3 adverse event results in severe or clinically significant, but not immediately life-threatening, consequences; results in hospitalization or prolonged hospitalization; disables an individual; and results in limitations on ability to bathe, dress, undress, feed, use the toilet, and take medications.

A Grade 2 event results in the need for moderate, minimal, or local or invasive intervention and results in limitations on age-appropriate ability to prepare meals, shop for groceries or clothes, use the telephone, and manage money.

⁶ The guidance for industry *Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events* discusses collecting delayed adverse event data in long-term follow-up for gene therapy trials.

V. AGREEMENT BETWEEN SPONSORS AND FDA ON A PLAN FOR SELECTIVE SAFETY DATA COLLECTION

A sponsor considering selective safety data collection should consult with the relevant FDA review division or divisions to determine whether such collection would be considered appropriate, and if so, develop its plan for implementation. The sponsor should discuss its specified plan with the relevant FDA review division or divisions at the appropriate time (e.g., at the end-of-phase 2 meeting for selective safety data collection for a phase 3 trial) to determine whether the plan is acceptable and to reach an agreement with the division or divisions on the details of the plan. The agreement should be incorporated into the procedures for safety data collection in the protocol, the monitoring plan, and other appropriate trial documents. These steps should help ensure consistent implementation across trial sites, help support risk-based monitoring efforts, and help alleviate potential inspectional problems related to safety data collection.